REMARKS

Reconsideration of this application as amended is respectfully requested.

Claims 11 to 21 are pending in this application. Claims 11 to 21 have been canceled and new claims 22 to 68 have been added.

Attorney for Applicants gratefully acknowledge the personal interview held between the undersigned and the Examiner on February 25, 1991. At the interview the pending Office Action as well as the references relied on therein were discussed. In addition, the more relevant references cited in the Information Disclosure Statement filed for this application on February 11, 1991 were discussed. It was pointed out that while the Watt, et al. and the Biaggioni, et al. references report experiments in humans, Biaggioni, et al. only looked at activation of the nervous system and Watt, et al. only measured coronary blood flow and ventricular function. Neither are directed to detecting and assessing the severity of any myocardial dysfunction. Based on this personal interview, Applicants are submitting new claims 22 to 68, as well as the following remarks.

With regard to the pending Office Action, on page 2 of said Action, claims 12 and 13 were rejected under 35 U.S.c. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The Examiner alleges that claims 12 and 13 are indefinite because it is not clear if the method is imaging to detect "the presence and assess the severity" or detect "the presence or assess the severity" of coronary artery disease in humans.

New claims 22 to 57 have been clarified so that they are now directed to detecting "the presence and assessing the

severity" of myocardial dysfunction, coronary artery disease or ventricular dysfunction in humans. It is respectfully submitted that this change overcomes the Examiner's rejection based on indefiniteness.

The Examiner has also rejected claims 12 to 16 and 18 to 21 under 35 U.S.C. §103 as being unpatentable over Crystal et al., "Small Vessel and Total Coronary Blood Volume During Intracoronary Adenosine", Amer. J. Physiol., 241(2), pg. 194-201 (1981) ("Crystal") either alone, or with regard to claims 16 and 17, in combination with Camici et al. "A Multitracer Autoradiographic Technique For Imaging Myocardial Flow and Metabolism", pp. 159-162 (1891) ("Camici").

With regard to Crystal alone, the Examiner alleges that this reference discloses a method in which adenosine causes a six-fold increase in myocardial blood flow and that adenosine is disclosed to cause vasodilation like papaverine, dipyridamole, norepinephrine or nitroglycerine. The Examiner further alleges that while Crystal does his work on pigs[1], not humans, he teaches that adenosine is a vasodilator and causes a myocardial blood flow increase. The Examiner also alleges that while Crystal is not assessing for the severity of vascular disease, he is assessing and one would assess and evaluate for the severity of vascular disease wherever the problem was suspected.

It is respectfully submitted that the Examiner's assertions are incorrect in that the present invention is not obvious in view of Crystal either alone or in combination with Camici.

With regard to the present method claims, the Examiner has the burden under section 103 to establish a prima facie case of obviousness. In re Fine, 5 U.S.P.Q 2d 1596, 1599 (Fed. Cir.

---

[1] The experiments in Crystal were actually carried out in dogs.

1988). In order to satisfy this burden some objective teaching in the prior art suggesting or teaching the modification of a reference which would result in the methods of the present applicant's invention must be shown Id. With regard to Crystal alone, it is not possible to meet this burden.

The methods of the present invention, which are claimed in new claims 22 to 68, concern methods for detecting myocardial dysfunction. More particularly, these methods involve detecting the presence and assessing the severity of coronary artery disease, ventricular dysfunction, and differences in blood flow through disease free coronary vessels and stenotic coronary vessels. These methods are to be practiced in humans. In practicing these methods, the first step to be carried out is administering to a human an amount of an adenosine receptor agonist sufficient to provide coronary artery dilation. The preferred adenosine receptor agonist is adenosine. It has been determined by applicants, through tests performed on humans, that the dosage of the adenosine receptor agonist needed to practice this novel method is from about 20 mcg/kg/minute to about 200 mcg/kg/minute, preferably about 140 mcg/kg/minute, by intravenous infusion. It has also been shown by applicants through tests performed in humans, that the adenosine receptor agonist also can be administered by intracoronary bolus injection is a dosage of about 2 mcg to about 20 mcg.

Thereafter, different techniques are followed depending on the information the person performing the tests is attempting to obtain.

If the tests are being performed to detect the presence and assessing the severity of coronary artery disease, then the next step is to inject a radiopharmaceutical agent into the human and then perform a radiopharmaceutical myocardial perfusion imaging technique in order to detect perfusion defects in the

coronary vessels of the human. Perfusion defects are an indication of coronary artery disease. Applicants have shown in Example 1 of the present application (which supplements Example 1 and 2 of the parent application serial no. 231,217) that this method compares favorably with methods which utilize a standard exercise protocol. In addition, Example 1 shows that this novel method is as safe and effective in humans as methods using a standard exercise protocol.

If the tests are being performed to detect ventricular dysfunction, the next step after the administration of the adenosine receptor agonist is to perform a ventricular function imaging on the human in order to detect said ventricular dysfunction. Applicants have shown in Example 2 of the present application that this method is also safe and effective when performed in humans.

If the tests are being performed to determine the difference between coronary blood flow through disease free coronary vessels and stenotic coronary vessels, the next step after administration of the adenosine receptor agonist, is to perform a method on the human for measuring coronary blood flow. This allows for the assessment of vasodilatory capacity (reserve capacity) of coronary vessels in humans. Applicants have shown in Example 3 of the present application that this method is safe and effective when performed in humans.

In contrast, Crystal discloses experiments performed in anesthetized dogs to determine small vessel and total coronary blood volume during intracoronary adenosine administration. In order to determine the results of these experiments, the dogs were sacrificed and myocardial tissue samples were evaluated. There is no mention of the dosage of adenosine administered to the anesthetized dogs or whether the anesthetized dog's coronary vessels were diseased or disease free. Crystal states that his

study was undertaken to examine the influence of adenosine on total coronary blood volume and on the relation of myocardial hematocrit to large vessel hematocrit. Based on the experiments performed the authors concluded that the infusion of adenosine into an anesthetized dog's coronary artery, which is perfused at constant pressure, causes relaxation of the smooth muscle of arteriolar resistance vessels and of other vessels larger than 100μm in diameter, and it has no effect on precapillary sphincters or small vessels. In addition, the Crystal reference states that adenosine caused no change in myocardial small vessel blood volume even though it caused a maximal increase in coronary blood flow along with an increase in total coronary blood volume. Crystal also states that adenosine caused a six-fold increase in myocardial blood flow that the authors attribute to dilation of the coronary resistance vessels or arterioles.

It is clear, based on the disclosure of Crystal, that this reference does not render the methods of the present invention prima facie obvious.

In the first instance, the Crystal reference only discloses detecting myocardial blood flow through larger coronary blood vessels as opposed to smaller coronary blood vessels, as well as detecting total coronary blood volume after intra-coronary adenosine administration. The Crystal reference contains absolutely no disclosure regarding whether the coronary vessels of the anesthetized dogs were diseased or disease free and thus there is no disclosure regarding testing in diseased coronary vessels or testing in order to detect coronary artery disease. The Examiner has admitted this on page 3 of the present Office Action, where he states that the Crystal reference does not disclose assessing for severity of vascular disease. In contrast, the methods of the present invention are specifically directed to detecting myocardial dysfunction, including coronary

artery disease, ventricular dysfunction, and defects in blood flow through stenotic coronary vessels.

In addition, Crystal only discloses that adenosine is a vasodilator that causes a six-fold increase in myocardial blood flow. Crystal makes no disclosure or suggestion of using adenosine in humans to detect and assess the severity of myocardial dysfunction or using adenosine in myocardial imaging. This is significant in that many compounds such as papavarine and nitroglycerine have been shown to be vasodilators, however these compounds have no role in detecting myocardial dysfunction or myocardial imaging. In contrast, applicants have shown by specific examples that adenosine receptor agonists such as adenosine can be used effectively in humans to detect the presence and assess the severity of coronary artery disease, ventricular dysfunction and determine the difference in blood flow through disease free and stenotic coronary vessels.

Furthermore, Crystal makes absolutely no disclosure regarding the amount of adenosine administered to the anesthetized dogs. The reference only states that the adenosine was infused at a rate sufficient to cause maximal dilation. This is in contrast to applicant's invention where it has been determined, through tests performed in humans, that the adenosine receptor agonist should be administered in a dosage of about 20 mcg/kg/minute to about 200 mcg/kg/minute by intravenous infusion or about 2 mcg to about 20 mcg by intracoronary bolus injection, in order to avoid the unpredictability and adverse effects associated with these compounds.

In additon, the Crystal reference only discloses administering adenosine by intracoronary infusion. In contrast, the novel methods of the present invention include the administration of an adenosine receptor agonist by various routes when it is used to detect and assess the severity of myocardial

dysfunction. These routes include intravenous infusion, intracoronary infusion, intravenous bolus injection, and intracoronary bolus injection.

Moreover, the experiments performed in Crystal included experimentally controlled and constant coronary perfusion pressure. This differs significantly from the methods of the present invention and from a clinical setting in which coronary perfusion pressure is not constant and may be affected by the systemic hemodynamic effects of the adenosine receptor agonist.

In addition to not specifically disclosing applicant's invention, the authors of the Crystal reference make no suggestion that the method they disclose can be used to detect myocardial dysfunction more particularly, detecting the presence and assess the severity of coronary artery disease, ventricular disfunction or to determine the difference in blood flow through disease free as opposed to stenotic coronary vessels in humans as applicants have shown. The Crystal reference also does not suggest any dosage of adenosine to be administered or administering adenosine by intravenous infusion or intracoronary bolus injection. Furthermore, there is no suggestion that another agent besides adenosine could be used. Based on this, the Examiner's reliance on In re O'Farrell, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988) is misplaced.

In O'Farrell, the patent applicant's method for producing predetermined protein in stable form in a host species of bacteria through genetic engineering, was found to be obvious under 35 U.S.C. §103. This finding was based on a reference, authored by two of the three patent applicant's which contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that the modification would be successful.

The Crystal reference does not satisfy the above requirements of O'Farrell to show obviousness. There is no enabling methodology in Crystal for practicing the novel methods of the present invention. Furthermore, since there is no suggestion in Crystal of the methods of the present invention, there could be no evidence suggesting that the methods of the present invention would be successful. The Examiner is using hindsight to create a disclosure in a prior art reference where none exists. This has been strictly prohibited by the Federal Circuit. W.L. Gore & Associates, Inc. v. Garlock, Inc., 220 U.S.P.Q. 303,312 (Fed. Cir. 1983) cert. denied, 469 U.S. 851 (1984).

In addition to the above described differences, the methods of the present invention are also not prima facie obvious over Crystal since the method disclosed in Crystal was performed in anesthetized dogs, whereas the methods of the present invention are performed on humans. Furthermore, Crystal does not suggest that the method it discloses could be used in humans.

This distinction is important in that adenosine has been reported to have adverse effects when used in dogs. This has discouraged its use in humans in techniques related to those disclosed in the present application. This is supported by statements made by researchers studying the use of adenosine in humans. For example, in an article by Wilson et al., entitled "Effects of Adenosine on Human Coronary Arterial Circulation",[2] the authors state at page 1596:

> Despite the widespread use of adenosine in animal studies, concern over adenosine-induced hypotension and heart block have hampered its use in humans. In dogs, intravenous doses sufficient to produce maximal coronary dilation also results in a

---

[2] Circulation, Vol. 82, No. 5, pp. 1595-1606, (1990). This reference has been cited in an Information Disclosure Statement filed previously.

> significant fall in systemic arterial blood pressure. In addition, large doses of adenosine increase the refractory period of the sinoatrial and atrioventricular nodes and can result in heart block. A preliminary study using intracoronary adenosine in humans revealed a strikingly high incidence of adenosine-induced conduction block in the atrioventricular node. Id. at 1596.

In addition, in an article by Zijlstra et al. entitled "Value and Limitations of Intracoronary Adenosine for the Assessment of Coronary Flow Reserve",[3] with regard to the use of adenosine in humans, the authors state at page 79:

> . . . several characteristics of adenosine limit its practical applicability. First, the dose needed to induce maximal hyperemia varies widely from patient to patient and seems unpredictable. This makes adenosine an unsuitable agent for coronary vasodilation if a radiographic technique is used to measure coronary flow reserve. Second, three of our 12 patients developed bradyarrhythmias immediately following adenosine administration in a dose close to that needed to produce adequate hyperemia. Although these bradyarrhythmias were short-lasting, they produced discomfort for the patients and precluded a meaningful interpretation of the coronary-flow-velocity data after this adenosine injection. the bradyarrhythmic effects of intracoronary adenosine are in accordance with its well-known electrophysiologic effects when administered intravenously.
>
> In conclusion, the authors state:
>
> Intracoronary adenosine is a potent and very short-acting vasodilator. However, its clinical applicability is limited by side effects and unpredictability of the dose needed to induce a maximal hyperemic response in the coronary circulation.

---

[3] Catheterization and Cardiovascular Diagnosis, 15: pg. 76-80 (1988). This reference has been cited in an Information Disclosure Statement filed previously.

Furthermore, in editorial comments entitled "Adenosine, Renewed Interest in an Old Drug,"[4] the authors Pantely et al. state at page 1854:

> . . . Despite these interesting characteristics, adenosine never achieved clinical usefulness; rather it found a staid, but secure, role over the years as a short-acting vasodilating agent in experimental animals.

Even though two of these three references were published after the filing date of the present application and all three are not prior art, they show that people skilled in the art before and after the date of the present invention did not think adenosine could be utilized in humans for the uses related to those disclosed in the present application because of adenosine's unpredictability and adverse effects.[5]

In contrast, applicants have shown by specific examples that by utilizing the novel methods of the present invention adenosine can be administered to humans and that it is safe and effective. In particular, examples 1, 2 and 3 of the present application shows that adenosine can be used safely and effectively in humans to detect vascular disease. In particular, the methods of the present invention are useful in detecting the presence and assessing the severity of coronary artery disease, detecting the presence and assessing the severity of ventricular dysfunction and determining the difference between blood flow through disease free as opposed to stenotic coronary vessels. Thus, applicants' novel methods go against the teaching in the art.

---

[4] Circulation, 82: 1854-1856 (1990). This reference has been cited in an Information Disclosure Statement filed previously.

[5] A reference with a date of publication after the filing date of an application can be used to show the state of the art existing on the filing date of the application. Application of Hogan, 194 U.S.P.Q. 527, 537 (C.C.P.A. 1977).

The conventional wisdom in the art, as well as references published before and after the filing date of the present application, taught against using adenosine in humans for uses related to those disclosed in the present application. The above described statements made by researchers which expressed disbelief that the novel methods of the present invention would work in humans indicates that applicant's invention is nonobvious. U.S. v. Adams, 148 U.S.P.Q. 479, 484 (1966). Furthermore, if the prior art teaches away from the claimed invention this indicates the invention is not prima facie obvious. In re Dow Chemical, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988).

Furthermore, data obtained from anesthetized dogs after the administration of adenosine is not predictive of the effects of adenosine administration on unanesthetized humans. This is because there is significant variability with regard to the effects of adenosine administration in different species, and even different members of the same species. In addition, data obtained from anesthetized dogs after adenosine administration is not predictive of the effects of adenosine on unanesthetized humans because of differences in neurohormonal and autoregulatory control, as well as the fact that anesthesia would mask symptomatic complaints and adverse effects in humans.

In conclusion, Crystal does not disclose or suggest the novel methods of the present invention. Furthermore, the conventional wisdom in the art as well as references published before and after the filing date of the present application teach away from the methods of the present invention. Thus, the novel methods disclosed in the present application are not prima facie obvious over Crystal.

The Examiner has also rejected claims 12 to 16 and 18 to 21 over Crystal by alleging that while Crystal does not

disclose that the adenosine is naturally occurring, produced as a synthetic molecule, attached to a carrier molecule or administered as a saline solution, it is obvious because these are all standard procedures for administering an agent and are normally used by one of ordinary skill in the art. Furthermore, the Examiner has rejected canceled claims 20 and 21 alleging that Crystal discloses administering adenosine intra-arterially by infusion, and that while Crystal does not disclose the use of a bolus injection, it is well known that adenosine can be injected either by infusion or bolus injection. Regarding the amount of agent used, the Examiner alleges that it is experimentally obvious to administer an appropriate amount of agent to elicit the desired effect according to the object of the study.

It is respectfully submitted that the Examiner's assertions are incorrect regarding the route and composition by which the adenosine receptor agonist is administered, and the amount of compound administered.

Dependent claims are nonobvious under section 103 if the independent claims from which they depend are non-obvious. Hartness Int'l, Inc. v. Simplimatic Eng'r Co., 2 U.S.P.Q.2d 1826, 1831 (Fed. Cir. 1987). In new claims 22 to 48 applicants do not have independent claims directed to routes by which the adenosine receptor agonist is administered, the amount of compound administered or the composition by which they are administered. All claims regarding administering adenosine receptor agonists, the amount of the compounds administered and the compositions administered to humans are dependent on the independent claims directed to the novel methods of the present invention. Thus, applicants are claiming that when the novel methods of the present invention are practiced on humans, the adenosine receptor agonist is administered by intravenous infusion, intracoronary

infusion, intravenous bolus injection or intracoronary bolus injection depending on the novel method. In addition, applicants are claiming that when the novel methods of the present invention are practiced on humans, the amount of adenosine receptor agonist administered is about 20 mcg to about 200 mcg/kg/minute, (preferably 140 mcg/kg/minute) when given by intravenous infusion and about 2 mcg to about 20 mcg when given by intracoronary bolus injection. With regard to the compositions administered, applicants are claiming that when the novel methods of the present invention are practiced on humans, the adenosine receptor agonist can be administered in any type of composition that would be appropriate to a person skilled in the art.

Since the novel methods of the present invention are not obvious, administering an adenosine receptor agonist by the above described routes of administration, in the above-described amounts and in available compositions, when using these novel methods is also not obvious. Based on this, it is respectfully submitted that this rejection should be withdrawn.

The Examiner has also rejected claims 16 and 17 under 35 U.S.C. §103 as being unpatentable over Crystal in view of Camici. The Examiner alleges that Camici discloses the use of thallium-201 in clinical cardiology. The Examiner then goes on to allege that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use thallium-201 with Crystal's method because this tracer is frequently used in clinical cardiology for the diagnosis of myocardia ischemia and infarction.

It is respectfully submitted that the Examiner has not shown prima facie obviousness as to applicants claimed method with regard to these two references. Thus, this ground for rejection should be withdrawn.

With regard to the methods of the present invention, prima facie obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. In re Geiger, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987). Furthermore, the claimed invention taken as a whole cannot be said to be prima facie obvious without some reason given in the prior art as to why one of ordinary skill would have been prompted to combine the teachings of the references to arrive at the claimed invention. In re Regel, 188 U.S.P.Q. 136 (C.C.P.A. 1975). With regard to the Crystal and Camici references, there is no teaching or suggestion to combine them.

Camici discloses a technique for the simultaneous assessment of myocardial distribution of different isotopes in the same tissue specimen by autoradiography. The experiments undertaken in Camici were performed in anesthetized dogs. These experiments involved injecting three different radioactive tracers into the dog; killing the dog; and then sectioning the dog's heart to determine myocardial distribution of the radioactive tracers. One of the tracers used was thallium-201 which is described in Camici as an extractable, diffusible tracer frequently used in clinical cardiology for the diagnosis of myocardial ischemia and infarction. The Camici reference does not disclose or suggest utilizing a coronary vasodilator such as an adenosine receptor agonist when performing these experiments. In two of the experiments performed in Camici, an artificial stenosis (alleged to be capable of reducing resting coronary blood flow) was applied to the left anterior descending coronary artery allegedly in order to produce regional myocardial ischemia. This was followed by an intravenous bolus injection of thallium-201. Camici states that this artificial stenosis resulted in practically negligible concentrations of thallium-201

in the area of the left ventricle, which was supplied with blood by the artificially stenosed left anterior descending coronary artery.

Thus, Camici only discloses performing experiments in anesthetized dogs utilizing radioactive tracers and autoradiography to detect myocardial blood distribution. The results of these experiments were obtained by sacrificing the dogs and evaluating tissue samples. There is no disclosure or suggestion that these tests would be effective if performed in humans or that a coronary vasodilator such as an adenosine receptor agonist should be used in conjunction with these tests. Furthermore, the Camici reference only discloses detecting thallium defects in regions subserved by an artificial coronary stenosis that Camici alleges reduces resting coronary blood flow. This is in contrast to the methods of the present invention which compare resting blood flow, ventricular function or cardiac images to blood flow, ventricular function or cardiac images after a pharmacological stressor such as adenosine is administered.

With regard to the Crystal reference, as discussed at pages 13 to 16 of the present amendment, it discloses experiments performed in anesthetized dogs to determine small vessel and large vessel blood flow as well as total coronary blood volume during intracoronary adenosine administration. There is no disclosure regarding whether the coronary vessels of the anesthetized dogs were diseased or disease free and thus no disclosure or suggestion of administering adenosine to humans to assist in detecting coronary artery disease, ventricular dysfunction or differences between coronary blood flow through disease free coronary vessels as compared to stenotic coronary vessels. In addition, Crystal discloses experiments performed to detect resting coronary blood flow whereas the methods of the

present invention involve detecting blood flow, ventricular function or cardiac images after the administration of a pharmacological stressor such as adenosine. Furthermore, there is no disclosure or suggestion in Crystal to use thallium-201 in conjunction with autoradiography and adenosine in humans in order to detect the above described myocardial and vascular diseases.

In conclusion, there is no teaching, suggestion or incentive in either Crystal or Camici that these references could be combined so as to arrive at the novel methods of the present invention. Furthermore, even if it was possible to combine these two references, they still would not disclose utilizing an adenosine receptor agonist used in conjunction with invasive and non-invasive techniques to detect the presence and assess the severity of myocardial and vascular disease in humans, as claimed in the present application. The Examiner has not established prima facie obviousness with regard to these two references. Thus, this ground for rejection should be withdrawn.

The Examiner has also made four other references of record. However, the Examiner has not relied on these references and only alleges they are pertinent to Applicant's disclosure. It is respectfully submitted that these references are not pertinent to the present application.

The first of these references is U.S. Patent No. 4,709,703 to Lazarow et al. This reference discusses a radiologic imaging system and method using radiopaque microspheres for evaluating organ tissue perfusion. An adenosine solution is administered into an intracardiac catheter to provide vasodilation. Applicants do not believe this reference is relevant.

The second of these references is U.S. Patent No. 4,689,041 to Corday et al. This reference discusses a method and system for retrograde delivery of fluids containing a

pharmacologic or diagnostic agent. This reference does not mention the uses of an adenosine receptor agonist. Applicants do not believe this reference is relevant.

The third of these references is Hayden et al., "Scintiphotographic Studies of Acquired Cardiovascular Disease", Seminars in Nuclear Medicine, Vol. 3, No. 2, pgs. 177-190 (1973). This reference discusses utilizing radionuclide angiocardiography after the administration of 99^{m} Tc-pertechnetate to identify cardiovascular lesions. There is no mention of the use of an adenosine receptor agonist. Applicants do not believe this reference is relevant.

The fourth of these references is Kwan et al., "Photoaffinity Labeling of Adenosine Transporter in Cardiac Membranes with Nitrobenzylthioinosine", Am. J. Physiol., 246(5), pgs. 710-715 (1984). This references discloses studying the kinetic and molecular properties of the adenosine transporter in guinea pig cardiac membranes using nitrobenzylthioinosine. Applicants do not believe this reference is relevant.

On February 11, 1991, Applicants filed an Information Disclosure Statement. This Information Disclosure Statement contains references cited against the European application which corresponds to the present application, as well as other references recently obtained. Identification of these references is not to be construed as an admission by applicants or applicant's attorneys that such references are available as prior art against the subject application.

With regard to the Information Disclosure Statement, for the following reasons, the cited references, do not anticipate or render the claims of the present invention prima facie obvious.

The first cited reference is Strauss, et al., "Noninvasive Detection of Subcritical Coronary Arterial Narrowing

with a Coronary Vasodilator and Myocardial Perfusion Imaging", American Journal of Cardiology, Vol. 39, pg. 403-406 (1977) ("Strauss"). This reference was cited in the European Search Report issued for the present application's European counterpart. Strauss discloses experiments performed on anesthetized dogs utilizing ethyl adenosine-5-carboxylate and myocardial perfusion imaging wherein the radiopharmaceutical agent used was thallium-201. The experiments involved snaring a small segment of the anesthetized dog's left circumflex coronary artery, in order to, as the authors allege, create an artificial subcritical coronary stenosis. Thereafter, the anesthetized dogs were administered ethyl adenosine-5-carboxylate intravenously in a bolus dose of 1 mg/kg. Thallium-201 was then administered to the anesthetized dog and myocardial perfusion imaging was performed on the dog in order to determine myocardial blood perfusion. This was done by sacrificing the animal and evaluating tissue samples. The author states that based on this imaging, there was a decrease in tracer concentration in the zone of the left ventrical supplied by the snared left circumflex coronary artery.

The authors of Strauss allege that the results of their experiments could be applied to patients to assist in detecting subcritical coronary arterial lesions. However, they also concluded that the sensitivity and specificity of their technique remained to be determined in humans under clinical conditions.

The reference to Strauss would not anticipate nor render the novel methods of the present invention prima facie obvious. In order to show anticipation, a single reference must teach (i.e., identically describe) each and every step of the claims. Atlas Powder Co. v. E.I. DuPont deNemours & Co., 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). With regard to prima facie obviousness of the methods of the present invention, as stated previously, there must be some objective teaching in the prior

art to modify a reference to obtain applicant's claimed invention. In re Fine, 5 U.S.P.Q. 2d at 1598. Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure. In re Dow Chemicals, 5 U.S.P.Q. 2d at 1531. Furthermore, if the accepted wisdom in the art leads away from the claimed invention, this is strong evidence of nonobviousness. In re Hedges, 228 U.S.P.Q. 685 (Fed. Cir. 1986). It is clear the Strauss reference satisfies neither of these criteria.

There are significant differences between the Strauss reference and the novel methods of the present invention. Strauss discloses performing experiments in anesthetized dogs as opposed to the novel methods of the present invention which are to be carried out in humans. While Strauss alleges that the method he uses could be tried in humans, he also states that whether this would work or not would have to be determined under clinical conditions. As discussed at pages 17 to 20 of the present amendment, the conventional wisdom in the art prior to and even after the filing of the present application taught that adenosine could not be used in humans for uses related to those disclosed in the present application because of its unpredictability and adverse effects. Thus, applicant's discovery that adenosine receptor agonists could be used successfully in humans in the novel methods of the present invention, went against the conventional wisdom in the art.

In addition, as discussed previously, data obtained from anesthetized dogs after the administration of adenosine is not predictive of the effects of adenosine administration on unanesthetized humans. This is because there is significant variability with regard to the effects of adenosine administration in different species, and even different members of the same species. In addition, data obtained from

anesthetized dogs after adenosine administration is not predictive of the effects of adenosine on unanesthetized humans because of differences in neurohormonal and autoregulatory control, as well as the fact that anesthesia would mask symptomatic complaints and adverse effects in humans.

Furthermore, in Strauss, ethyl adenosine-5-carboxylate was administered to the anesthetized dogs by a bolus injection of 1 mg/kg. This is much greater than the range of 2 mcg to 20 mcg of the specified adenosine receptor agonist given by intracoronary bolus injection in the methods of the present invention. Moreover, the present invention includes administering the adenosine receptor agonist by intravenous infusion at a dosage of about 20 mcg/kg/minute to about 200 mcg/kg/minute, preferably about 140 mcg/kg/minute. There is no disclosure or suggestion in Strauss that the ethyl adenosine-5-carboxylate could be administered as an intravenous infusion.

In addition, the Strauss reference discloses snaring a small segment of the anesthetized dog's left circumflex coronary artery, in order to, as the authors allege, create an artificial subcritical coronary stenosis. This artificially induced stenosis poorly reflects the complex clinical setting of an atherosclerotic vessel occlusion in which vasomotor tone, neurohormonal regulation, adenosine receptor sensitivity and effector responsiveness may differ substantially. Thus, it is not possible to predict from the animal experiments performed in Strauss, the safety and efficacy of an adenosine receptor agonist such as adenosine in unanesthetized humans with vascular disease.

There is also additional support for a finding of the nonobviousness of the present invention in view of Strauss. The Strauss reference was published in March, 1977. Between that date and the filing of the present application there are no references of record, and applicant are not aware of any

references, which describe or suggest the successful use of the novel methods of the present invention in humans. This gap of more than 10 years between the date of the Strauss reference and the filing of the present application indicates that those skilled in the art did not think it was feasible to use these novel methods in humans. This also indicates the nonobviousness of the claimed invention. Fromson v. Advance Offset Plate, Inc., 225 U.S.P.Q. 26, 32 (Fed. Cir. 1985).

For the above described reasons, applicants believe that the Strauss reference would not anticipate or render prima facie obvious, the novel methods of the present invention.

The second reference cited in the concurrently filed Information Disclosure Statement is to Rumberger, et al. entitled "Use of Ultrafast Computed Tomography to Quantitate Regional Myocardial Perfusion: A Preliminary Report" ("Rumberger").[6] This reference was also cited in the European Search Report issued for the present application's European counterpart. This reference discloses preliminary experiments performed in anesthetized dogs to quantify regional myocardial perfusion utilizing adenosine, radiolabelled microspheres and rapid acquisition computed axial tomography. The experimental results were determined after sacrificing the animals and evaluating tissue samples. There is no mention that the anesthetized dogs used in this study had coronary artery disease. The authors allege adenosine is used to produce intermediate and maximal coronary vasodilation during the experiments. The reference states that the ability to noninvasively assess regional myocardial perfusion and flow reserve would significantly aid in the diagnosis and treatment of patients with heart disease and that the method they disclose offers promise for the quantification of regional myocardial

---

[6] Journal of the American College of Cardiology, Vol. 9, No. 1, pp. 59-69 (1987).

perfusion and myocardial flow reserve in patients. However, the reference also states that "although the preliminary theoretical and experimental studies are encouraging, they have raised a number of questions related to technical, theoretical and practical limitations related to the application of this method to quantification of regional myocardial perfusion in man."

There are significant reasons why this reference would not anticipate or render obvious the novel methods of the present invention. The Rumberger reference does not state whether the anesthetized dogs used in the experiments had diseased or disease-free coronary vessels even though the authors allege their methods might be able to be used in the diagnosis and treatment of patents with heart disease. The authors only state that the experiments were performed to quantify regional myocardial perfusion. In contrast, the novel methods of the present invention are specifically directed to detecting the presence and assessing the severity of coronary artery disease, ventricular dysfunction or differences in blood flow through disease-free and stenotic coronary vessels. In addition, applicants novel methods are performed in humans, whereas the experiments performed in Rumberger were performed in anesthetized dogs. This is significant in that, as discussed on page 17 to 20 of the present amendment, experimental results administering adenosine to anesthetized dogs does not mean adenosine can be used effectively in humans in the methods of the present invention. Furthermore, the Rumberger reference only states that adenosine was administered to the anesthetized dogs in order to provide intermediate and maximum vasodilation. Thus, Rumberger was only using adenosine as a vasodilator to validate the technique he was utilizing, and not to assist in detecting the presence and assess the severity of myocardial dysfunction. As discussed previously, just because a compound is useful as a

vasodilator does not mean the compound would be useful to detect myocardial dysfunction. In contrast, adenosine is used in the methods of the present invention to create an imbalance in perfusion between disease-free and stenotic coronary vessels, in order to detect perfusion deficits and to detect the presence and assess the severity of myocardial dysfunction. Based on these differences, applicants believe that this reference would not anticipate or render obvious the novel methods of the present invention.

The references numbered 3, 10, 11 and 12 in the concurrently filed Information Disclosure Statement are being brought to the Examiner's attention because they were also cited against the present application's European counterpart. Applicants do not believe these references are relevant and cite them only to satisfy their duty of disclosure.

Reference number 4 cited in the concurrently filed Information Disclosure Statement is authored by Biaggioni et al. This reference discusses the intravenous administration of adenosine in a dosage of 10 mcg/kg/minute to 140 mcg/kg/minute in man. The authors concluded that adenosine administration in conscious man is associated with activation of the sympathetic nervous system. This reference only discloses tests performed to determine the properties of adenosine and the effects the compound has when it is administered to humans. These effects include a decrease in diastolic blood pressure, an increase in heart rate, an increase in systolic blood pressure and an increase in plasma norepinephrine. Applicants also do not believe this reference is relevant and cite it only to satisfy their duty of disclosure.

Reference number 5 cited in the concurrently filed Information Disclosure Statement is authored by Hellman et al. This reference discloses experiments performed in anesthetized

dogs to determine the effect of an intracoronary bolus injection of adenosine-5-carboxylate hydrochloride on myocardial flow after artificial acute coronary artery occlusion, as determined by a radioactive microsphere technique. The experimental results were determined after sacrificing the animals and evaluating tissue samples. The authors alleged that the result of their study showed that ethyl adenosine-5-carboxylate significantly increased myocardial blood flow and decreased vascular resistance to both acutely ischemic, collateral dependent and normal areas of canine myocardium. Applicants do not believe this reference is relevant and cite it only to satisfy their duty of disclosure.

Reference number 6 cited in the concurrently filed Information Disclosure Statement is authored by Watt et al. This reference discloses tests performed in humans to determine the effects of adenosine on coronary blood flow and left ventricular function in man. The tests were performed on patients who were shown to have no significant stenosis at coronary arteriography and no other obvious cardiovascular disease. The authors concluded that their tests allegedly showed adenosine increases coronary flow in man and that adenosine-induced changes in coronary blood flow are transient and might be usefully applied in the measurement of coronary flow reserve, as an alternative to atrial pacing or intravenous dipyridamole. The intravenous bolus injections used caused chest pain so severe that the 8.5 mg. dose was omitted in three subjects. Applicants do not believe this reference is relevant. Furthermore applicants believe this reference is not available as prior art and cite it only out of an abundance of caution.

The references numbered 7 to 9 in the concurrently filed Information Disclosure Statement have been relied on by applicants in the present amendment at pages 17 to 20.

For the foregoing reasons, Applicants respectfully submit that the claims of the present application are in condition for allowance.

Respectfully submitted,

Date: February 7, 1997

20,823
Gerald J. Flintoft (Reg. No.)

PENNIE & EDMONDS
1155 Avenue of the Americas
New York, New York 10036-2711

(212) 790-9090